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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C08F 230/08, 220/28, 220/58

A1

(11) International Publication Number: WO 98/30615

(43) International Publication Date: 16 July 1998 (16.07.98)

(21) International Application Number: PCT/GB98/00070

(22) International Filing Date: 12 January 1998 (12.01.98)

(30) Priority Data:

9700390.9	10 January 1997 (10.01.97)	GB
9718909.6	5 September 1997 (05.09.97)	GB

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

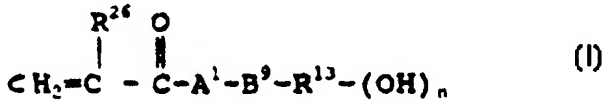
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

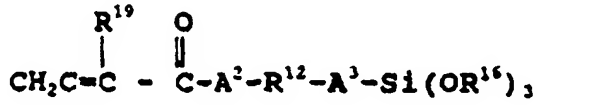
(54) Title: POLYMERS

(57) Abstract

A cross-linkable polymer is formed from monomers including a) a hydroxyl-group containing monomer of general formula (I) in which R^{26} is hydrogen or C_{1-4}-alkyl group, A^1 is -O- or $-NR^{27}-$ where R^{27} is hydrogen or a C_{1-4}-alkyl group or a group B^9 R-$(OH)_n$; B^9 is a bond, a straight or branched alkylene, an oxaalkylene or oligooxa alkylene group; R^{13} is a n + 1 functional (optionally substituted) C_{1-24} alkylene group, n is an integer of one or more; and b) a reactive monomer of general formula (II) in which R^{19} is hydrogen or a C_{1-4}-alkyl group or A^2 is -O- or $-NR^{21}-$ where R^{21} is hydrogen, or a C_{1-4}-alkyl group, R^{12} is C_{1-24} straight or branched alkylene, oxaalkylene or oligo oxaalkylene group in which each alkylene group has 1 to 6 carbon atoms, A^3 is a band or -O-, each R^{16} independently selected from C_{1-6}-alkyl groups. Preferably the polymer includes zwitterionic monomer and is useful for providing stable biocompatible coatings on substrates.



(I)



(II)

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POLYMERS

This invention relates to new polymeric materials especially suitable for use in biomedical applications, and processes for their production and use.

According to the present invention there is provided a crosslinkable polymer formed from monomers including

a) a hydroxyl-group containing monomer of the general formula I

I

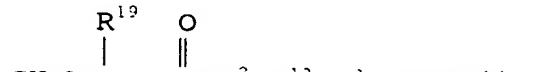
in which R^{26} is hydrogen or C_{1-4}-alkyl group A^1 is -O- or -NR^{27}- where R^{27} is hydrogen or a C_{1-4}- alkyl group or a group B^9 $R-(OH)_n$;

B^9 is a bond, a straight or branched alkylene, a oxa alkylene or oligooxa alkylene group;

R^{13} is a n + 1 functional (optionally substituted) C_{1-24} alkylene group,

n is an integer of one or more; and

b) a reactive monomer of the general formula (II)



II

in which R^{19} is hydrogen or a C_{1-4}-alkyl group or A^2 is -O- or -NR^{21}- where R^{21} is hydrogen, or a C_{1-4}-alkyl group

R^{12} is C_{1-24} straight or branched alkylene, oxaalkylene or oligo oxaalkylene group in which each alkylene group has 1 to 6 carbon atoms

A^3 is a band or -O-

each R^{16} independently selected from C_{1-6}-alkyl groups.

In hydroxyl group containing monomer of the general formula I, R^{26} is preferably hydrogen or methyl, most preferably methyl. A^1 is preferably -O-. B^9 is preferably a bond.

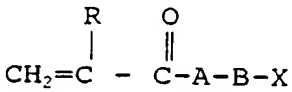
R^{13} is preferably selected from C_{2-6}-alkylene groups, most preferably C_{2-4}-alkylene, most preferably propylene.

The monomer I may consist of a mixture of compounds having different groups R^{13}. Preferably, in such a mixture, all groups R^{13} have the same number of carbon atoms, but may comprise a mixture of different isomers. For instance where the group R^{13} is propylene, it may consist of a mixture of 1,2-propylene and 1,3-propylene.

In the reactive monomer of the general formula II, R^{19} is preferably selected from hydrogen and methyl groups, most preferably R^{19} is methyl. A^2 is preferably -O-. A^3 is preferably -O-. R^{12} is preferably C_{2-6}-alkylene, preferably C_{2-4}-alkylene. Again, the monomer of the formula II may comprise a mixture of compounds having different groups R^{12}.

R^{16} is selected from C_{1-6}-alkyl groups, preferably C_{1-2}-alkyl groups.

Preferred polymers are made from monomers including a zwitterionic monomer of the general formula III



III

wherein B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X contains a carbon-carbon chain between B and the zwitterionic moiety or if Y contains a terminal carbon atom bonded to B, a valence bond;

X is a zwitterionic group

R is hydrogen or a C_1-C_4 alkyl group; and

A is -O- or $-NR^1-$ where R^1 is hydrogen or a C_1-C_4 alkyl group or R^1 is -B-X where B and X are as defined above.

In compounds of formula (III) it is preferred that K and B contain up to 12 carbon atoms in total.

In the zwitterionic monomer of the general formula III, R is preferably selected from hydrogen and methyl, and is most preferably methyl.

Preferably B^9 is an alkylene group of formula $-(CR^3_2)_a-$, wherein the groups $-(CR^3_2)-$ are the same or different, and in each group $-(CR^3_2)-$ the groups R^3 are the same or

different and each group R^3 is hydrogen, fluorine or C_{1-4} alkyl or fluoroalkyl, preferably hydrogen, and a is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

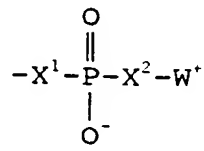
an oligo-oxaalkylene group of formula $-[(CR^4_2)_bO]_c(CR^4_2)_b-$ where the groups $-(CR^4_2)-$ are the same or different and in each group $-(CR^4_2)-$ the groups R^4 are the same or different and each group R^4 is hydrogen, fluorine or C_{1-4} alkyl or fluoroalkyl, preferably hydrogen, and b is from 1 to 6, preferably 2 or 3 and c is from 2 to 11, preferably 2 to 5; or

if X contains a carbon-carbon chain between B and the centre of permanent positive charge or if Y contains a terminal carbon atom, a valence bond.

Preferred groups B include alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms optionally containing one or more fluorine atoms.

Preferred zwitterionic groups on zwitterionic monomer III are groups in which the cationic moiety is based on a quaternary ammonium group and the anionic moiety is based on a phosphate group. Preferred zwitterionic groups are ammonium phosphate ester zwitterionic groups. Preferably the ammonium is quaternary ammonium and the phosphate group is a diester group, or amide analogue. Usually the cationic group is located at the end of pendant group X distant from B.

Preferably X is a group of formula



(VI)

in which the moieties X^1 and X^2, which are the same or different, are -O-, -S-, -NH- or a valence bond, preferably -O-, and W^+ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the

anionic and cationic moieties which is preferably a C_{1-12}-alkylene group.

Preferably W contains as cationic group an ammonium group, more preferably a quaternary ammonium group.

The group W^+ may for example be a group of formula $-W^1-N^+R^{23}{}_3$, $-W^1-P^+R^{23a}{}_3$, $-W^1-S^+R^{23a}{}_2$ or $-W^1-Het^+$ in which:

W^1 is alkylene of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl, alkylene aryl, aryl alkylene, or alkylene aryl alkylene, disubstituted cycloalkyl, alkylene cycloalkyl, cycloalkyl alkylene or alkylene cycloalkyl alkylene, which group W^1 optionally contains one or more fluorine substituents and/or one or more functional groups; and either

the groups R^{23} are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl or two of the groups R^{23} together with the nitrogen atom to which they are attached form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{23} together with the nitrogen atom to which they are attached form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups R^{23} is substituted by a hydrophilic functional group, and

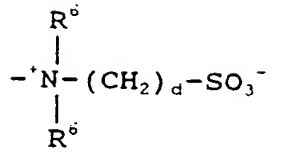
the groups R^{23a} are the same or different and each is R^{23} or a group OR^{23}, where R^{23} is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine.

Preferably W^1 is a straight-chain alkylene group, most preferably 1,2-ethylene.

Most preferred groups are the groups of formula (IVA), (IVB), (IVC), (IVD) and (IVE) as defined below: monomers containing such groups may be used alone or in combination with further zwitterionic monomers to provide a copolymer. Of these groups (IVB) are particularly preferred.

The groups of formula (IVA) are:



(IVA)

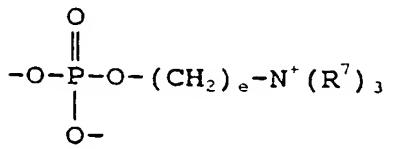
where the groups R^6 are the same or different and each is hydrogen or C_{1-4} alkyl and d is from 2 to 4.

Preferably the groups R^6 are the same. It is also preferable that at least one of the groups R^6 is methyl, and more preferable that the groups R^6 are both methyl.

Preferably d is 2 or 3, more preferably 3.

When X is a group of formula (IVA) preferably B is a group of formula $-(CR^3_2)-$ or $-(CR^3_2)_2-$, eg. $-(CH_2)-$ or $-(CH_2CH_2)-$.

The groups of formula (IVB) are:



(IVB)

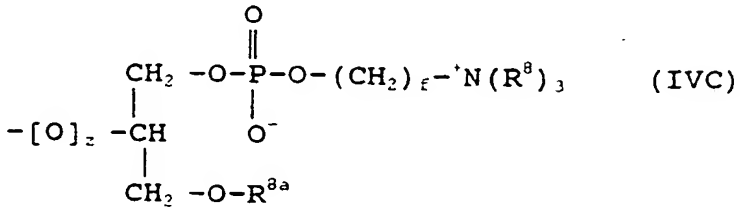
where the groups R^7 are the same or different and each is hydrogen or C_{1-4} alkyl, and e is from 1 to 4.

Preferably the groups R^7 are the same. It is also preferable that at least one of the groups R^7 is methyl, and more preferable that the groups R^7 are all methyl.

Preferably e is 2 or 3, more preferably 2.

When X is a group of formula (IVB) preferably B is a group of formula $-(CR^3_2)-$ or $-(CR^3_2)_2-$, eg. $-(CH_2)-$ or $-(CH_2CH_2)-$.

The groups of formula (IVC) are:



(IVC)

wherein the groups R^8 are the same or different and each is hydrogen or C_{1-4} alkyl, R^{8a} is hydrogen or, more preferably, a group $-C(O)R^{8b}$ where R^{8b} is hydrogen or methyl,

preferably methyl, B^1 is a valence bond or straight or branched alkylene, oxaalkylene or oligo-oxaalkalyene group, and f is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is O, if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1.

Preferably the groups R^8 are the same. It is also preferable that at least one of the groups R^8 is methyl, and more preferable that the groups R^8 are all methyl.

Preferably f is 1 or 2, more preferably 2.

Preferably B^1 is:

a valence bond;

an alkylene group of formula $-(CR^{3a}_2)_{aa}-$, wherein the groups $-(CR^{3a}_2)-$ are the same or different, and in each group $-(CR^{3a}_2)-$ the groups R^{3a} are the same or different and each group R^{3a} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

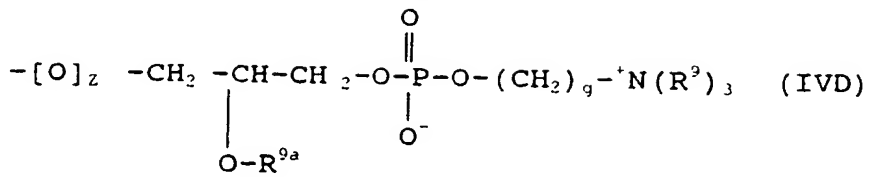
an oligo-oxaalkylene group of formula $-[(CR^{4a}_2)_{ba}O]_{ca}-$ where the groups $-(CR^{4a}_2)-$ are the same or different and in each group $-(CR^{4a}_2)-$ the groups R^{4a} are the same or different and each group R^{4a} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ba is from 1 to 6, preferably 2 or 3, and ca is from 1 to 12, preferably 1 to 6.

Preferred groups B^1 include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms.

Preferably B and B^1 are the same.

When X is a group of formula (IVC) preferably B is a group of formula $-[(CR^4_2CR^4_2)_cO_b]CR^4_2CR^4_2-$, eg. $-(CH_2CH_2O)_c(CH_2CH_2)-$.

The groups of formula (IVD) are:



(IVD)

wherein the groups R^9 are the same or different and each is hydrogen or C_1-C_4 alkyl, R^{9a} is a hydrogen or, more preferably, a group $-C(O)B^2R^{9b}$, R^{9b} is hydrogen or methyl, preferably methyl, B^2 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and g is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is O if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1.

Preferably the groups R^9 are the same. It is also preferable that at least one of the groups R^9 is methyl, and more preferable that the groups R^9 are all methyl.

Preferably g is 1 or 2, more preferably 2.

Preferably B^2 is:

a valence bond;

an alkylene group of formula $-(CR^{3b}_2)_{ab}-$, wherein the groups $-(CR^{3b}_2)-$ are the same or different, and in each group $-(CR^{3b}_2)-$ the groups R^{3b} are the same of different and each group R^{3b} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ab is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6, carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

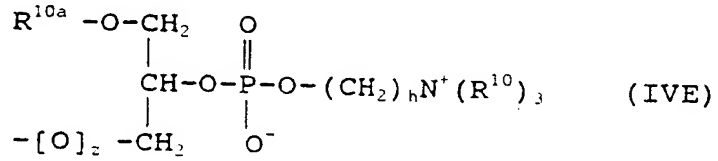
an oligo-oxaalkylene group of formula $-[(CR^{4b}_2)_{bb}O]_{cb}-$ where the groups $-(CR^{4b}_2)-$ are the same or different and in each group $-(CR^{4b}_2)-$ the groups R^{4b} are the same or different and each group R^{4b} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and bb is from 1 to 6, preferably 2 or 3, and cb is from 1 to 12, preferably 1 to 6.

Preferred groups B^2 include a valence bond and alkylene, oxalkylene and oligo-oxalkylene groups of up to 12 carbon atoms.

Preferably B and B^2 are the same.

When X is a group of formula (IVD) preferably B is a group of formula $-[(CR^4_2CR^4_2)_bO]_cCR^4_2CR^4_2-$, eg. $-(CH_2CH_2O)_cCH_2CH_2-$.

The groups of formula (IVE) are:



(IVE)

wherein the groups R^{10} are the same or different and each is hydrogen or C_{1-4} alkyl, R^{10a} is hydrogen or, more preferably, a group $-C(O)B^3R^{10b}$ where R^{10b} is hydrogen or methyl, preferably methyl, B^3 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and h is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is O if X is directly bonded to the oxygen or nitrogen and otherwise Z is 1.

Preferably the groups R^{10} are the same. It is also preferable that at least one of the groups R^{10} is methyl, and more preferable that the groups R^{10} are all methyl.

Preferably h is 1 or 2, more preferably 2.

Preferably B^3 is:

a valence bond;

an alkylene group of formula $-(CR^{3c}_2)_{ac}-$, wherein the groups $-(CR^{3c}_2)-$ are the same or different, and in each group $-(CR^{3c}_2)-$ the groups R^{3c} are the same or different and each group R^{3c} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ac is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

an oligo-oxaalkylene group of formula

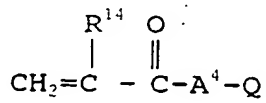
$-[(CR^{4c}_2)_{bc}O]_{cc}-$ where the groups $-(CR^{4c}_2)-$ are the same or different and in each group $-(CR^{4c}_2)-$ the groups R^{4c} are the same or different and each group R^{4c} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and bc is from 1 to 6, preferably 2 or 3, and cc is from 1 to 12, preferably 1 to 6.

Preferred groups B^3 include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms.

Preferably B and B^3 are the same.

When X is a group of formula (IVE) preferably B is a group of formula $-[(CR^4_2CR^4_2)_bO]_cCR^4_2CR^4_2-$, eg. $-(CH_2CH_2O)_cCH_2CH_2-$.

A polymer according to the invention is preferably formed from monomers including a comonomer of the formula V



V

in which R^{14} is hydrogen or a C_{1-4}-alkyl group

A^4 is -O- or $-NR^{15}-$ where R^{15} is hydrogen, C_{1-4}-alkyl group or a group Q,

and Q is selected from hydroxyl groups

a straight or branched alkyl, alkoxyalkyl or (oligo-alkoxy)alkyl chain containing 1 to 24 carbon atoms unsubstituted or substituted by one or more fluorine atoms and optionally containing one or more carbon-carbon double or triple bonds;

a siloxane group $-(CR^{16a}_2)_{qq}\ (SiR^{16b}_2)\ (OSiR^{16b}_2)_{pp}R^{16b}$ in which each group R^{16a} is the same or different and is hydrogen or alkyl of 1 to 4 carbon atoms or aralkyl, for example benzyl or phenethyl, each group R^{16b} is alkyl of 1 to 4 carbon atoms, qq is from 1 to 6 and pp is from 0 to 49; and

C_{1-24}-alkyl groups substituted with a group Q^5 selected from anionic groups selected from carboxylate, sulphonate, hydrogenphosphate and phosphate groups and cationic groups

selected from $-N^+R^{31}_3$ in which each group R^{31}_3 in which each group R^{31} is the same or different, and is hydrogen or alkyl of 1 to 6 carbon atoms two of which groups R^{31} may together from a heterocyclic ring containing from 5 to 7 atoms, ^+N Het where Het is an unsaturated heterocyclic group substituted or unsubstituted by one or more alkyl groups of 1 to 4 carbon atoms, and groups $P^+R^{32}_3$ in which each group R^{32} is the same or different and is hydrogen or alkyl of 1 to 6 carbons atoms, two of which groups R^{32} may together form a heterocyclic ring containing from 5 to 7 atoms.

In the formula V, group R^{14} is preferably selected from hydrogen and methyl. A^4 is preferably -O-.

In the monomer of formula V, the group Q is most conveniently a hydrophobic group, preferably an alkyl, a fluoroalkyl or a siloxane group.

Preferred monomers V are comonomers in which Q is

a) an alkyl group which group optionally contains one or more etheric oxygen atoms and optionally one or more carbon-carbon double or triple bonds for instance which has 6 or more carbon atoms, or

b) a fluoroalkyl group, preferably of 6 or more carbon atoms, which group optionally contains one or more etheric oxygen atoms and optionally one or more carbon-carbon double or triple bonds, or

c) a siloxane group, containing up to 50 silicon atoms, preferably in a linear chain.

Preferably the alkyl or fluoroalkyl groups Q contains up to 24 carbon atoms, for instance up to 18 carbon atoms. For instance in the compound of the formula V, Q is a straight or branched alkyl, alkoxyalkyl or oligoalkoxyalkyl chain containing 1-24 carbon atoms, unsubstituted or substituted by one or more fluorine atoms and optionally containing one or more carbon-carbon double or triple bonds or is a siloxane group as defined above.

Most preferably Q is:

an alkyl group of formula $-(CR^{17}_2)_mCR^{17}_3$, wherein the groups $-(CR^{17}_2)-$ are the same or different, and in each

group $-(CR^{17}_2)-$ the groups R^{17} are the same or different and each group R^{17} is hydrogen, fluorine or C_{1-4} alkyl or fluoroalkyl and m is from 5 to 23 if Q contains no fluorine atoms or from 1 to 23, preferably 5 to 23, if Q contains one or more fluorine atoms;

an alkoxyalkyl having 1 to 12 carbon atoms in each alkyl moiety; unsubstituted or substituted by one or more fluorine atoms; or

an (oligo-alkoxyl) alkyl group of formula $-[(CR^{18}_2)_nO]_o(CR^{18}_2)_nR^{18}$ where the groups $-(CR^{18}_2)-$ are the same or different and in each group $-(CR^{18}_2)-$ the groups R^{18} are the same or different and each group R^{18} is hydrogen, fluorine or C_{1-4} alkyl or fluoroalkyl and n is from 2 to 6, preferably 3 to 4, and o is from 1 to 12.

Particularly preferred groups Q are straight chain alkyl or fluoroalkyl groups optionally containing one or more carbon-carbon double or triple bonds.

Where Q is a siloxane group as defined above, each group $-(CR^{16a}_2)-$ may be the same or different, preferably the same, and preferably each group R^{16a} is hydrogen. Preferably qq is from 2 to 4, and is most preferably 3. Each group $-(SiR^{16b}_2)-$ may be the same or different, preferably the same, and preferably each group R^{16b} is methyl. Preferably pp is from 4 to 29.

In one specific embodiment the group Q does not contain any ethylenic unsaturation, i.e. any carbon-carbon double or triple bonds.

Particular examples of comonomers containing an alkyl, fluoroalkyl or siloxane group include: methylmethacrylate, butylmethacrylate, n-dodecyl methacrylate, octadecyl methacrylate, hexadecyl methacrylate, 1H,1H,2H,2H-heptadecafluorodecyl methacrylate, p-octyl styrene, p-dodecyl styrene and monomethacryloxypropyl terminated siloxanes especially poly(dimethyl siloxanes). n-Dodecyl methacrylate is particularly preferred.

In the novel polymers, it is preferred that all of the groups R^{16}, R^{17}, R and R^{14} represent the same meaning,

preferably methyl. Preferably also the groups A^1, A^2, A and A^4 represent the same group, and are preferably, -O-. Where such common features are present in the monomers, it is believed that copolymerisation proceeds in an optimum fashion, since the monomers are likely to have similar reactivity ratios.

The polymers are made from their constituent monomers by radical polymerisation, typically using thermal, redox or photochemical initiation. The polymerisation conditions could be such that reaction between the silyl group of monomer of the formula II with the hydroxyl group of the monomer of the formula I does not take place to any significant extent during polymerisation.

For thermal polymerisation a temperature from 40 to 100°C, typically 50 to 80°C is used. For photochemical polymerisation actinic radiation such as gamma, U.V., visible, or microwave radiation may be used. Typically U.V. radiation of wavelength 200 to 400 nm is used.

The polymerisation is generally performed in a reaction medium, which is for instance a solution or dispersion of the monomers in a liquid phase using as a solvent for example acetonitrile, dimethyl formamide, chloroform, dichloromethane, ethyl acetate, dimethyl sulphoxide, dioxan, benzene, toluene, tetrahydrofuran, or where the polymer does not contain groups which react with protic solvents, water or an alkanol containing from 1 to 4 carbon atoms, e.g. methanol, ethanol or propan-2-ol. Alternatively, a mixture of any of the above solvents may be used.

The polymerisation may be carried out in the presence of one or more polymerisation initiators, usually free radical generators, usually peroxides or azo initiators, such as benzoyl peroxide, 2,2'-azo-bis(2-methylpropionitrile) or benzoin methyl ether. Other polymerisation initiators which may be used are disclosed in "Polymer Handbook", 3rd edition, Ed. J. Brandrup and E.H. Immergut, Pub. Wiley-Interscience, New York, 1989.

Generally the polymerisation is performed for 1 to 72 hours, preferably 8 to 48, for instance 16 to 24 hours, and under an inert atmosphere of for example nitrogen or argon. The polymer is generally purified by dialysis, precipitation in a non-solvent (e.g. diethyl ether or acetone) or ultrafiltration. The resulting polymer is generally dried under vacuum, eg. for 5 to 72 hours and has a molecular weight from 10,000 to 10 million, preferably from 20,000 to 1 million.

It is preferable for the monomer of the formula I to be present in a molar excess to the monomer of the formula II. The two monomers are generally provided in the polymer in amounts so as to give the desired level of crosslinking when the polymer is used. Preferably the molar ratio of the monomer of the formula I to the monomer of the formula II is in the range 1:2 to 10:1, preferably 1:1 to 10:1, most preferably 2:1 to 6:1.

Where a zwitterionic monomer of the formula III is included, it is generally contained in a molar quantity in the range 0.01%, preferably at least 1%, most preferably at least 5%, for instance at least 10%. The total amount is preferably less than 50%, for instance in the range 15 to 33%.

Where comonomer of the formula V is included in the polymer, it may be present in an amount in the range .01 to 99% by mole, most preferably in an amount in the range 1 to 95%, most preferably in the range 10 to 90%, for instance in the range 25 to 80%.

The amount of monomer of the formula II is generally at least 1%, preferably at least 2%, for instance in the range 3 to 10%. The amount of monomer of the formula I is generally higher than the molar amount of monomer of the formula II, since this tends to encourage complete reaction of the trialkoxy silyl group of the monomer of the formula II. The residual, uncrosslinked hydroxyl group of the monomer of formula I is not very reactive, so that its presence in the crosslinked product does not cause problems

with reactive interactions with fluids or solid substrates with which it is in contact.

The crosslinkable polymer is of particular utility for coating applications. The present invention provides further coating compositions containing the crosslinkable polymer. Such compositions generally comprise a liquid vehicle within which the polymer is dissolved or dispersed. Preferably the liquid vehicle includes a solvent for the polymer in which the polymer is dissolved. For instance the solvent may be an aqueous based solvent, but is more likely to be an organic solvent, for instance an alcohol or ether solvent. Coating compositions may comprise other components which assist wetting of an underlying surface and/or coating integrity.

The present invention provides also processes in which substrates are coated with a liquid coating composition according to the invention, followed by a step in which solvent is removed from the coating, for instance by evaporation, and in which the polymer is, after coating, subjected to a crosslinking step in which it is subjected to conditions in which crosslinking takes place between the hydroxyl groups of the monomer of the formula I and one of the said OR^{16} groups of monomer of the formula II. Such reaction conditions generally involve subjecting the polymer to raise temperature, for instance under reduced pressure to remove alcohol $R^{16}OH$ by-product.

For some coating processes, it may be desirable to polymerise the starting monomers and crosslink in a single step. In this case, a coating composition comprises monomers and, if necessary, a solvent for the monomers, and is subjected to conditions whereby reaction between the trialkoxysilyl group of monomer II and the hydroxyl group of monomer I takes place simultaneously with radical initiated polymerisation.

The use of monomers of the formula I in combination with the formula II gives very good crosslinking levels, whilst producing a polymer product which has good

integrity, that is cohesion, but adequate flexibility. It therefore provides a good coating for use on compliant substrates, especially substrates which are subjected to lengthening or other dimensional change in use. For instance the substrate which is coated may be the metal of a stent or other biomedical device which is expanded in use. The substrate may be an elastomer, or a plastically expandable plastics material.

The invention is illustrated further in the following examples:

Example 1

The following outlines an experiment concerning membranes with and without hydroxypropyl methacrylate (Hpm). The figures show the relative molar amounts.

Membranes prepared were:

../001 2-(methacryloyloxyethyl)-2'-(trimethylammonium ethyl) phosphate inner salt:lauryl methacrylate:3-trimethoxysilylpropyl methacrylate 30:60:10

../002 2-(methacryloyloxyethyl)-2'-(trimethylammonium ethyl) phosphate inner salt:lauryl methacrylate:3-trimethoxysilylpropyl methacrylate 32:63:5

../003 2-(methacryloyloxyethyl)-2'-(trimethylammonium ethyl) phosphate inner salt:lauryl methacrylate:3-trimethoxysilylpropyl methacrylate 33:65:2

../004 2-(methacryloyloxyethyl)-2'-(trimethylammonium ethyl) phosphate inner salt:lauryl methacrylate:3-trimethoxysilylpropyl methacrylate:hydroxypropyl methacrylate 29:59:2:10

../005 2-(methacryloyloxyethyl)-2'-(trimethylammonium ethyl) phosphate inner salt:lauryl methacrylate:3-trimethoxysilylpropyl

methacrylate:hydroxypropyl methacrylate 23:47:5:25.

Method:

Moulds were prepared by laminating glass sheets with polyethylene terephthalate (PET) film using spray mount. The moulds were assembled using a PTFE spacer. The monomer solutions were injected into the moulds and allowed to polymerise at 50C for 16 hours.

Observations:

Experiment /001 yielded polymer films on every occasion, however, the film obtained in each case was brittle and shattered on handling.

Experiment /002 on some occasions yielded a film that was isolable whilst on other occasions resulted in a tacky film which could not be removed from the PET even after swelling in water for 16 hours.

Experiment /003 consistently resulted in a tacky film which could not be removed from the PET.

Experiment /004 still continued to result in tacky films even with the inclusion of Hpm.

Experiment /005 gave clear films on every occasion which were elastic and exhibited some good wear and tear strength properties.

Example 2

This example illustrates a process in which the polymers are preformed and then coated. The polymerisation uses free radical solution polymerisation techniques following the standard method outlined below.

A triple-necked round bottom flask (250ml) was equipped with a Davis condenser, a nitrogen inlet, the, polymerisation solvent which is ethanol and a thermometer. The condenser was topped with a calcium chloride guard tube, and a magnetic follower was added to the flask. The reaction system then purged using nitrogen gas.

The zwitterionic monomer was weighed and then stirred in the reaction solvent until dissolved. The comonomers

were weighed and then stirred into the reaction solvent until dissolved. The initiator used throughout the polymer development was AIBN at a level of 2 w/w %, and this was dissolved into the reaction solvent.

The solutions were then filtered under vacuum using a buchner funnel, into the reaction vessel. The solution was degassed using a constant flow of nitrogen for a period of twenty minutes, after which time the nitrogen flow rate was reduced and the temperature increased to 62C. The polymerisation was carried out under an atmosphere of nitrogen, and maintained at 62C for

When the polymerisation had finished the heat source was removed and the solution was allowed to cool to room temperature. The solvent was removed using rotary evaporation techniques until the point at which the polymer began to foam. This solution was then further diluted with dichloromethane and precipitated by dropwise addition into acetone with constant stirring.

The precipitate was then collected using vacuum filtration under a blanket of nitrogen and dried at 25C in vacuo for 16 hours.

The polymer was then cooled using liquid nitrogen and ground to a fine powder using an analytical mill. The polymer was then further dried in vacuo at 25C for 16 hours. The yield of polymer obtained was recorded.

Ethanol was the reaction solvent.

The technique could be used to produce polymers having the molar ratios of example 1. When used to make a polymer having the monomer ratios of example 1/005, it produced a product having the following properties:

Elemental Analysis:

	C	H	N	P	Si
Theoretical	62.59	9.91	1.37	3.02	0.60
Actual	60.65	9.88	1.43	3.06	0.59

	Dilute Viscosity Measurements:		
Batch No.	Intrinsic Viscosity	Relative Viscosity	Mv
1	0.1455	1.145	172769
2	0.1404	1.140	1609190
3	0.1433	1.143	167718

Mv is Viscosity Average Molecular Weight and is expressed in Daltons.

The polymer was coated using dip coating from ethanol at 5 and 10 mg/ml. The coating speed was 3mm/min. The polymer was cross-linked by heating at 70C for 4 hours or longer eg overnight.

The polymer was then used to coat a number of steel coronary devices crosslinked by heating and submitted to a number of tests which looked at the performance of the hydrogel coating during *in vitro* testing.

All of the SEM microscopy was carried out using a Hitachi S4000 field emission SEM. The samples were prepared by mounting on the stubs using conductive graphite pads. Sputter coating was not used.

Molecular weight, radius of gyration and second virial coefficients for the polymers were calculated from Zimm plots obtained through the use of static light scattering. The measurements were made using a PL-LSP light scattering photometer starting at 30° and increasing in 15° increments. The polymers were measured in ethanol with toluene used as the reference. A refractometer was used to establish the dn/dc value for the solutions.

Fibrinogen adsorption uses an assay similar to that used in our application WO93/01221.

Results and Discussion

Molecular weights for the polymer was found to be in the region of 200,000 daltons, with a radius of gyration of 14 nm.

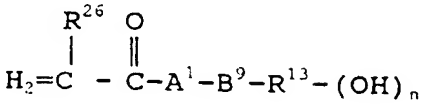
The biological performance (fibrinogen adsorption) of the novel polymers has been shown to be comparable to that of phosphorylcholine group containing copolymers currently used by Biocompatibles. The adsorption value was about 0.2 (comparative unit relating to absorbance in an ELISA test) for both PC polymers and about 1.8 for the uncoated steel.

An important property required of the final polymer coating is its mechanical stability. The angioplasty devices undergo several deformations and stresses when deployed, as such any coating must respond to these conditions. This is demonstrated in experiments, where coronary stents were coated with the hydroxyalkyl/reactive silyl copolymer and a more brittle coating not containing the hydroxypropyl methacrylate monomer. The more brittle polymer coating ruptures under the stresses associated with balloon expansion. This is not the case when stents coated with the new polymer are subjected to the procedure.

CLAIMS

1. A cross-linkable polymer formed from monomers including

a) a hydroxyl-group containing monomer of the general formula I



in which R^{26} is hydrogen or C_{1-4}-alkyl group;

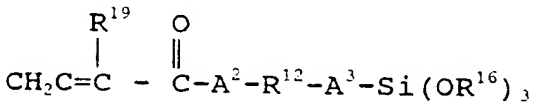
A^1 is -O- or $-NR^{27}-$ where R^{27} is hydrogen or a C_{1-4}-alkyl group or a group B^9 $R-(OH)_n$;

B^9 is a bond, a straight or branched alkylene, a oxa alkylene or oligooxa alkylene group;

R^{13} is a n + 1 functional (optionally substituted) C_{1-24} alkylene group, and

n is an integer of one or more;

b) a reactive monomer of the general formula (II)



II

in which R^{19} is hydrogen or a C_{1-4}-alkyl group;

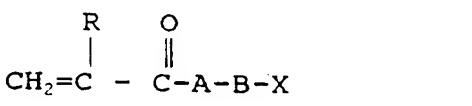
A^2 is -O- or $-NR^{21}-$ where R^{21} is hydrogen, or a C_{1-4}-alkyl group

R^{12} is C_{1-24} straight or branched alkylene, oxaalkylene or oligo oxaalkylene group in which each alkylene group has 1 to 6 carbon atoms;

A^3 is a bond or -O-; and

each R^{16} is independently selected from C_{1-6}-alkyl groups.

2. A polymer according to claim 1 in which the monomer includes a zwitterionic monomer of the general formula (III)



III

wherein B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated

chains or, if X contains a carbon-carbon chain between B and the zwitterionic moiety or if Y contains a terminal carbon atom bonded to B, a valence bond;

X is a zwitterionic group

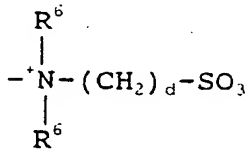
R is hydrogen or a C_1-C_4 alkyl group; and

A is -O- or $-NR^1-$ where R^1 is hydrogen or a C_1-C_4 alkyl group or R^1 is -B-X where B and X are as defined above.

3. A polymer according to claim 2 in which the zwitterionic group X is a group in which the cationic moiety is based on a quaternary ammonium group and the anionic moiety is based on a phosphate group, preferably ammonium phosphate ester zwitterionic groups.

4. A polymer according to claim 2 in which the zwitterionic group is selected from groups IVA, IVB, IVC, IVD and IVE in which the

i) groups of formula (IVA) are:

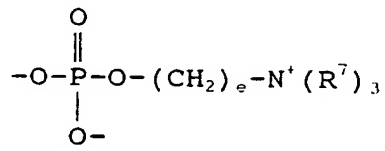


(IVA)

where the groups R^6 are the same or different and each is hydrogen or C_{1-4} alkyl and

d is from 2 to 4;

ii) the groups of formula (IVB) are:

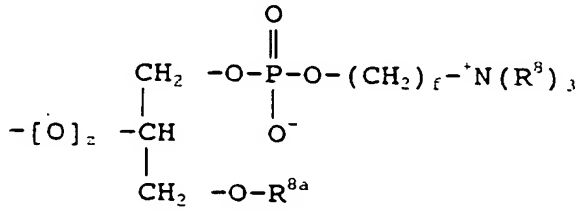


(IVB)

where the groups R^7 are the same or different and each is hydrogen or C_{1-4} alkyl, and

e is from 1 to 4;

iii) the groups of formula (IVC) are:



(IVC)

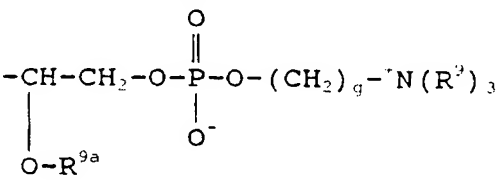
wherein the groups R^8 are the same or different and each is hydrogen or C_{1-4} alkyl,

R^{8a} is hydrogen or a group $-C(O)B^1R^{8b}$ where R^{8b} is hydrogen or methyl, preferably methyl,

B^1 is a valence bond or straight or branched alkylene, oxaalkylene or oligo-oxaalkalyene group, and f is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is O, if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1;

iv) the groups of formula (IVD) are:



(IVD)

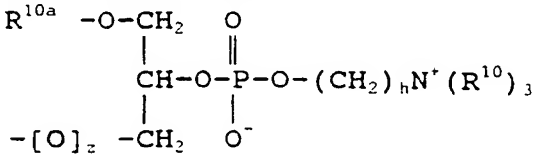
wherein the groups R^9 are the same or different and each is hydrogen or C_1-C_4 alkyl

R^{9a} is a hydrogen or a group $-C(O)B^2R^{9b}$, R^{9b} is hydrogen or methyl, preferably methyl,

B^2 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and g is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is O if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1;

v) the groups of formula (IVE) are:



(IVE)

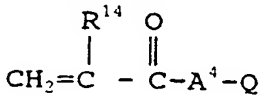
wherein the groups R^{10} are the same or different and each is hydrogen or C_{1-4} alkyl,

R^{10a} is hydrogen or methyl, preferably methyl,

B^3 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and h is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is O if X is directly bonded to the oxygen or nitrogen and otherwise Z is 1.

5. A polymer according to any preceding claim in which the monomers include a comonomer of the formula V



V

in which R^{14} is hydrogen or a C_{1-4}-alkyl group

A^4 is -O- or $-NR^{15}-$ where R^{15} is hydrogen, C_{1-4}-alkyl group or a group Q,

and Q is selected from hydroxyl groups;

a straight or branched alkyl, alkoxyalkyl or (oligo-alkoxy)alkyl chain containing 1 to 24 carbon atoms unsubstituted or substituted by one or more fluorine atoms and optionally containing one or more carbon-carbon double or triple bonds;

a siloxane group $-(CR^{16a}_2)_{qq}\ (SiR^{16b}_2)\ (OSiR^{16b}_2)_{pp}R^{16b}$ in which each group R^{16a} is the same or different and is hydrogen or alkyl of 1 to 4 carbon atoms or aralkyl, for example benzyl or phenethyl, each group R^{16b} is alkyl of 1 to 4 carbon atoms, qq is from 1 to 6 and pp is from 0 to 49, and

C_{1-24}-alkyl groups substituted with a group Q^5 selected from anionic groups selected from carboxylate, sulphonate, hydrogenphosphate and phosphate groups and cationic groups $-^+NR^{31}_3$ in which each group R^{31} is the same or different, and is hydrogen or alkyl of 1 to 6 carbon atoms two of which groups R^{31} may together from a heterocyclic ring containing from 5 to 7 atoms, ^+NHet where Het is an unsaturated heterocyclic group substituted or unsubstituted by one or more alkyl groups of 1 to 4 carbon atoms, and groups $P^+R^{32}_3$ in which each group R^{32} is the same or different and is hydrogen or alkyl of 1 to 6 carbons atoms, two of which

groups R^{32} may together form a heterocyclic ring containing from 5 to 7 atoms.

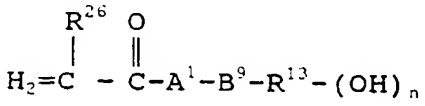
6. A coating composition comprising a liquid vehicle and a polymer according to claims 1 to 5 dissolved or dispersed in the vehicle.

7. A composition according to claim 6 in which the liquid vehicle includes a solvent for the polymer in which the polymer is dissolved.

8. A crosslinked polymer formed by subjecting a polymer according to any of claims 1 to 5 to condition such that cross-linking takes place between the OH group of monomer I and one of the said OR groups of monomer II.

9. A process of polymerising monomers including

a) a hydroxyl-group containing monomer of the general formula I



in which R^{26} is hydrogen or C_{1-4}-alkyl group;

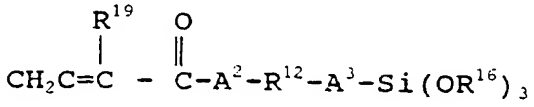
A^1 is -O- or $-NR^{27}-$ where R^{27} is hydrogen or a C_{1-4}-alkyl group or a group B^9 R-$(OH)_n$;

B^9 is a bond, a straight or branched alkylene, a oxa alkylene or oligooxa alkylene group;

R^{13} is a n + 1 functional (optionally substituted) C_{1-24} alkylene group; and

n is an integer of one or more; and

b) a reactive monomer of the general formula (II)



II

in which R^{19} is hydrogen or a C_{1-4}-alkyl group or;

A^2 is -O- or $-NR^{21}-$ where R^{21} is hydrogen, or a C_{1-4}-alkyl group;

R^{12} is C_{1-24} straight or branched alkylene, oxaalkylene or oligo oxaalkylene group in which each alkylene group has 1 to 6 carbon atoms;

A^3 is a bond or -O-; and

each R^{16} is independently selected from C_{1-6}-alkyl groups.

10. A process of cross-linking a polymer according to any of claims 1 to 5, in which the polymer is subjected to conditions such that cross-linking takes place between the OH group of monomer I and one of the said OR^{16} groups of monomer II.

11. A process according to claim 10 in which the polymer has been coated on a substrate prior to the cross-linking reaction.

12. A product comprising a substrate coated with a cross-linked polymer which is formed by crosslinking a polymer according to claim 9.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/00070

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08F230/08 C08F220/28 C08F220/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 412 385 A (PPG INDUSTRIES) 13 February 1991 see page 11; example 11 ---	1,5-12
X	EP 0 075 957 A (UNION CARBIDE) 6 April 1983 see claims 1,4-6,8-10 see examples 4,5 ---	1,5,9
X	DATABASE WPI Section Ch, Week 9403 Derwent Publications Ltd., London, GB; Class A14, AN 94-022958 XP002060534 & JP 05 331 251 A (KANSAI PAINT CO LTD) , 14 December 1993 see abstract --- -/--	1,5-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 1998	25/05/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte · Application No
PCT/GB 98/00070

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 9346 Derwent Publications Ltd., London, GB; Class A18, AN 93-365463 XP002060535 & JP 05 271 608 A (KANSAI PAINT CO LTD) , 19 October 1993 see abstract	1,5,9
X	DATABASE WPI Section Ch, Week 9312 Derwent Publications Ltd., London, GB; Class A14, AN 93-096841 XP002060536 & JP 05 039 375 A (CHISSO CORP) , 19 February 1993 see abstract	1,5-7,9
A	US 4 213 886 A (TURNER R. L.) 22 July 1980 see claims 1,4,5 see column 4, line 6 - column 6, line 46	1,5,9
A	FR 1 549 939 A (DOW CORNING) 13 December 1968 see example 4A	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/00070

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		JP 3070763 A	26-03-91
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EP 75957 A	06-04-83	CA 1186436 A	30-04-85
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FR 1549939 A	13-12-68	AT 294272 A	15-10-71
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